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Lovastatin versus placebo for the treatment of dengue in Vietnamese adults

Submission date
28/06/2012

Recruitment status
No longer recruiting

Registration date
24/07/2012

Overall study status
Completed

Last Edited
23/01/2019

Condition category
Infections and Infestations

[X] Prospectively registered

[X] Protocol

[_] Statistical analysis plan

[X] Results

[_] Individual participant data

Plain English summary of protocol

Background and study aims
Dengue is a mosquito-transmitted viral infection that represents a major public health problem in Vietnam and globally. The consequences range from a symptom-free infection through to life-threatening shock and bleeding. Severe dengue infection is often caused by inflammation of the lining of blood vessels (the endothelium). There is currently no treatment for dengue beyond supportive care. Lovastatin is part of a class of drugs called statins, which were initially developed as fat (lipid)-lowering agents but have been shown to have additional benefits. Studies suggest that their use appears to be associated with an improved outcome in critically ill patients. The additional benefits include reducing inflammation of the endothelium, which could translate into a beneficial effect in dengue. Furthermore, laboratory studies have shown that lovastatin may have additional antiviral properties. These properties together with its favourable safety and cost profile make lovastatin an attractive option for dengue treatment. The main aim of the study is to formally assess the safety of using statins in patients with dengue. The study will also provide an opportunity to investigate the effect of statins on the immune response to dengue, the dengue viral load and the clinical outcome of infection.

Who can participate?
All patients aged 18 or over with a clinical suspicion of dengue, less than 72 hours of fever and a positive rapid test for dengue non-structural protein 1 (NS1) will be eligible for recruitment into the study. We have a target sample size of 330 patients.

What does the study involve?
We propose to investigate the effect of lovastatin for 5 days in adult dengue patients presenting in the first 72 hours of illness. Patients will be randomly allocated to one of two groups: one group will take lovastatin and the other group will take a dummy drug (placebo). As this is the first study investigating statin therapy in dengue with a particular focus on safety, we will use a low dose of lovastatin with the first 30 patients. If this is found to be safe we will then increase the lovastatin dose for the next 30 patients.

What are the possible benefits and risks of participating?
This is the first study exploring the use of statins in dengue. In view of this, our study has a particular emphasis on safety. Statins are very widely used and have an excellent safety profile.

Rarely they can cause potentially serious problems with muscles and the liver. It is possible that these effects may occur more often in patients with dengue. We will therefore closely monitor patients to detect the development of adverse events early. In addition, patients may experience discomfort and bruising from the blood tests, although these would form part of the usual care for patients infected with dengue.
The study will pay the participants' hospital costs. If lovastatin has a beneficial effect this will potentially benefit the patients taking lovastatin as well as future patients, and will potentially benefit the community given the prevalence of dengue in Vietnam.

Where is the study run from?
The Hospital for Tropical Diseases in Ho Chi Minh City, Vietnam.

When is the study starting and how long is it expected to run for?
Patients will be recruited over two dengue seasons (2012 and 2013). The study started in November 2012 and is expected to end in January 2015.

Who is funding the study?
The Wellcome Trust (UK)

Who is the main contact?
Dr James Whitehorn
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Contact information

Type(s)
Scientific

Contact name
Dr James Whitehorn

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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
26DX

Study information

Scientific Title
A pilot study to investigate short-course lovastatin therapy in Vietnamese adults with dengue

Study objectives
The study hypothesis is that lovastatin is safe as a short course therapy for acute dengue infections in Vietnamese subjects. This study is intended to provide preliminary information to assist in designing a possible future trial powered to assess efficacy as well as safety in the same population.

On 15/11/2012 the overall trial start date was changed from 15/07/2012 to 13/11/2012.

On 20/05/2015 the overall trial end date was changed from 15/01/2015 to 18/02/2015.

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. Oxford Tropical Research Ethics Committee, 06/06/2012, OxTREC reference: 68-11
2. Hospital for Tropical Diseases Committee of Scientific and Medical Ethics, 14/03/2012, Reference Number: CS/ND/12/09

Study design
Randomized double-blind placebo-controlled trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details below to request a patient information sheet

Health condition(s) or problem(s) studied
Dengue disease

Interventions
Current interventions as of 15/11/2012:
Patients will be assigned to one of two treatment arms:
Active Medicinal Product:
1. COHORT 1 - 40 mg lovastatin once daily for up to 5 days

2. COHORT 2 - 80 mg lovastatin once daily for up to 5 days
OR
Placebo: visually matched placebo once daily for up to 5 days

The first dose will be given as soon as practically possible after enrolment. If patients are discharged before the completion of 5 days, study drug will be stopped on this day.
The study drug will be stopped if platelets fall below 5 x 10^9/L or if the patient develops severe bleeding

Previous interventions until 15/11/2012:
Patients will be assigned to one of two treatment arms:
Active Medicinal Product:
1. COHORT 1 - 40 mg lovastatin once daily for up to 5 days
2. COHORT 2 - 80 mg lovastatin once daily for up to 5 days
OR
Placebo: visually matched placebo once daily for up to 5 days

The first dose will be given as soon as practically possible after enrolment. If patients are discharged before the completion of 5 days, study drug will be stopped on this day.

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Lovastatin

Primary outcome measure
To evaluate the safety and tolerability of lovastatin in adult patients with dengue including rate of adverse events in each cohort

Secondary outcome measures
1. Disease progression as defined by one or more of the following:
1.1. Admission to intensive care unit
1.2. Diagnosis of shock (see definition)
1.3. Development of severe bleeding (see definition)
1.4. CNS involvement
1.5. Death
2. Fever clearance time (defined as the time from enrolment to the first time the temperature falls to < 37.5 degree C and remains below this level for 48 hours)
3. Plasma viraemia - AUC day 3 - 6 (log10-transformed)

Additional experimental endpoints include:
2. Haematological, biochemical and physiological abnormalities:
2.1. Platelet nadir between day 3 and 8 of illness
2.2. Maximum haematocrit between day 3 and 8 of illness
2.3. Percentage increase in haematocrit between day 3 and 8 of illness from baseline
2.4. Maximum alanine aminotransferase (ALT) and Creatine kinase (CK) recorded between day 3 and 8 of illness

2.5. Lowest oxygen saturation recorded between day 3 and 8 of illness
2.6. Number of patients in each group requiring colloid
3. Quality of life scores from visual analog scale during treatment (quantifiable self-measurement of quality of life in relation to personal health)
4. Virological safety parameters:
4.1. Duration from enrolment to the first undetectable viremia measurement
4.2. Duration from enrolment to first negative NS1 measurement

Overall study start date
13/11/2012

Completion date
18/02/2015

Eligibility

Key inclusion criteria
1. Age > 18
2. Clinical suspicion of dengue
3. <72 hours of fever
4. Positive rapid test for dengue non-structural protein 1
5. Informed consent or assent to participate in the trial

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
330

Key exclusion criteria
Patients with one or more of the following criteria at enrolment will be excluded from the study:
1. Signs or symptoms suggestive of any other acute infectious disease
2. Alanine aminotransferase (ALT) >150 U/L
3. Creatine kinase (CK) >1000 U/L
4. Myopathy
5. Cirrhosis
6. Use of statins within 1 week
7. Chronic use of medication contraindicated for use with lovastatin (cholestyramine, isradipine, warfarin, amiodarone, azole antifungals, fibrates, colchicine, ciclosporin, danazol, macrolides, nefazodone, niacin (high doses), protease inhibitors, verapamil, diclofenac, doxycycline, imatinib, isoniazid, nicardipine, propofol, quinidine, and diltiazem)

8. Pregnancy and lactation (all females of childbearing potential must provide urine for a âHCG test)
9. Platelet levels below 50 x 10^9/L (added as of 15/11/2012)

Date of first enrolment
13/11/2012

Date of final enrolment
21/01/2015

Locations

Countries of recruitment
Viet Nam

Study participating centre
Oxford University Clinical Research Unit
Ho Chi Minh City
Viet Nam
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Sponsor information

Organisation
University of Oxford (UK)

Sponsor details
Clinical Trials & Research Governance
Joint Research Office
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Churchill Hospital
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Sponsor type
University/education

ROR
https://ror.org/052gg0110

Funder(s)

Funder type
University/education

Funder Name
Wellcome Trust (UK) ref: 097430/Z/11/Z

Alternative Name(s)

Funding Body Type
Private sector organisation

Funding Body Subtype
International organizations

Location
United Kingdom

Funder Name
Oxford University Clinical Research Unit (UK)

Results and Publications

Publication and dissemination plan
Not provided at time of registration

Intention to publish date

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article	protocol	31/10/2012		Yes	No
Results article	results	15/02/2016	23/01/2019	Yes	No